

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Kenji Fukudome and Charles T. Esmon

Express Mail Label No.:
EL 273 004 882 US

Serial No.: Divisional of 08/182,616

Art Unit: Not Yet Assigned

Filed: August 20, 1999

Examiner: Not Yet Assigned

For: *CLONING AND REGULATION OF AN ENDOTHELIAL CELL PROTEIN
C/ACTIVATED PROTEIN C RECEPTOR*



Assistant Commissioner for Patents
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

Sir:

Pursuant to 37 C.F.R. §1.56 and 37 C.F.R. §1.97, Applicants submit an Information Disclosure Statement, including fourteen (14) pages of Form PTO-1449. The documents cited were cited by or submitted to the Patent Office in Application Serial No. 09/182,616, filed , 1998, to which the present application claims priority. Pursuant to 37 C.F.R. §1.98(a), Applicants are not enclosing copies of these publications. Copies will be provided upon request, however.

OMRF 152 DIV(3)
20487/242

This Information Disclosure Statement is being filed under 37 C.F.R. § 1.97(b) prior to a first Office Action on the merits. It is believed that no fee is required with this submission. However, should a fee be required, the Commissioner is hereby authorized to charge any required fees to Deposit Account No. 01-2507.

U.S. Patents

<u>Number</u>	<u>Issue Date</u>	<u>Patentee</u>	<u>Class/Subclass</u>
3,625,214	12-07-1971	Higuchi	128/260
4,244,946	01-13-1981	Rivier	424/177
4,305,872	12-15-1981	Johnston, et al.	260/112.5R
4,316,891	02-23-1982	Guilleman, et al.	424/177
4,629,784	12-16-1986	Stammer	530/328
4,789,734	12-06-1988	Pierschbacher	530/395
4,782,137	11-01-1988	Hopp, et al.	530/328
4,792,525	12-20-1988	Ruoslahti, et al.	435/240.243
4,906,474	03-06-1990	Langer, et al.	424/428
4,925,673	05-15-1990	Steiner, et al.	424/455
4,980,286	12-25-1990	Morgan, et al.	
5,009,889	04-23-1991	Taylor, et al.	424/94.64
5,298,599	03-29-1994	Rezaie, et al.	530/350
5,695,993	12-09-1997	Fukudome, et al.	435/325
5,698,189	12-16-1997	Rowe, et al.	474/78.08
5,749,968	05-12-1998	Melanson, et al.	118/300
5,779,673	07-14-1998	Roth, et al.	604/101
5,804,392	09-08-1998	Esmon, et al.	435/7.1

Foreign Documents

<u>Number</u>	<u>Publication Date</u>	<u>Patentee</u>	<u>Country</u>
WO 96/05303	02-22-1996	Okla. Med. Res. Found.	PCT
WO 96/20732	07-11-1996	Chiron Viagene	PCT
WO 96/21470	07-18-1996	Genemedicine, Inc.	PCT
WO 98/20041	05-14-1998	Okla. Med. Res. Found	PCT

Publications

ABE, et al., "Granulocyte proteases and hydrogen peroxide synergistically inactive thrombomodulin of endothelial cells in vitro," *J. Lab. Clin. Med.* 123(6):874-881 (1994).

ACCP/SCCM Consensus Conference, "Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis," *Chest* 101(6):1644-1655 (1992).

AGRAWAL, et al., "Oligodeoxynucleoside phosphoramidates and phosphorothioates as inhibitors of human immunodeficiency virus," *Proc. Natl. Acad. Sci. USA* 85(19):7079-7083 (1988).

AREND, et al., "Building of IL-1 α , IL-1 β , and IL-1 Receptor Antagonist by Soluble IL-1 Receptors and Levels of Soluble IL-1 Receptors in Synovial Fluids," *J. Immunol.* 153:4766-4774 (1994).

ASAKURA, et al., "Plasma Levels of Soluble Thrombomodulin Increase in Cases of Disseminated Intravascular Coagulation With Organ Failure," *Am. J. Hematol.* 38:281-287 (1991).

ASKEW, et al., "Molecular Recognition with Convergent Functional Groups, 6, Synthetic and Structural Studies with a Model Receptor for Nucleic Acid Components", *J. Am. Chem. Soc.*, 111:1082-1090 (1989).

BANGALORE, et al., "High affinity binding sites for activated protein C and protein C on cultured human umbilical vein endothelial cells. Independent of protein S and distinct from known ligands," *Thromb Haemos* 72(3):465-74 (1994).

BERG, et al., "Aberrant RNA splicing of the protein C and protein S genes in health individuals," *Blood Coag Fibrinol.* 7:625-631 (1996).

BLUME, et al., "Triple helix formation by purine-rich oligonucleotides targeted to the human dihydrofolate reductase promoter," *Nucleic Acids Res.* 20(7):1777-84 (1992).

BOCK, "Active Site Selective Labeling of Serine Proteases with Spectroscopic Probes Using Thioester Peptide Chloromethyl Ketones: Demonstration of Thrombin Labeling Using N^{α} -[(Acetylthio)acetyl]-D-Phe-Pro-Arg-CH₂Cl," *Biochemistry* 27:6633-6639 (1988).

BOEHME, et al., "Release of thrombomodulin from endothelial cells by concentrated action of TNF- α and neutrophils: *in vivo* and *in vitro* studies," *Immunology* 87:134-140 (1996).

BOURIN & LINDAHL, "Review Article: Glycosaminoglycans and the regulation of blood coagulation," *Biochem. J.* 289:313-330 (1993).

CLACKSON, et al., "Making antibody fragments using phage display libraries," *Nature* 352:624- 688 (1991).

CONWAY & ROSENBERG, "Tumor Necrosis Factor Suppresses Transcription of the Thrombomodulin Gene in Endothelial Cells," *Mol. Cell. Biol.* 8(12):5588-5592 (1988).

COONEY, et al., "Site-specific oligonucleotide binding represses transcription of the human c-myc gene in vitro," *Science*. 241(4864):456-9 (1988).

CROOKE, et al., "Progress toward oligonucleotide therapeutics: pharmacodynamic properties," *FASEB J.* 7(6):533-9 (1993).

CURTIS, et al., "IL-1 and its receptor are translocated to the nucleus," *J. Immunol.* 144:1295-1303 (1990).

DAHLBÄCK, "Inhibition of Protein C_a Cofactor Function of Human and Bovine Protein S by C4b-binding Protein," *J. Biol. Chem.* 261(26):12022-12027 (1986).

DAHLBÄCK, "Protein S and C4b-Binding Protein: Components Involved in the Regulation of the Protein C Anticoagulant System," *Thromb. Haemostas.* 66:49-61 (1991).

DAUGHERTY, et al., "Polymerase chain reaction facilitates the cloning, CDR-grafting, and rapid expression of a murine monoclonal antibody directed against the CD18 component of leukocyte integrins," *Nucl. Acids Res.* 19(9):2471-2476 (1991).

DITTMAN & MAJERUS, "Structure and Function of Thrombomodulin: A Natural Anticoagulant," *Blood* 75(2):329-336 (1990).

DITTMAN, "Thrombomodulin - Biology and Potential Cardiovascular Applications," *Trends Cardiovasc. Med.* 1(8):331-336 (1991).

DREYFUS, et al., "Treatment of Homozygous Protein C Deficiency and Neonatal Purpura Fulminans with a Purified Protein C Concentrate," *N. Engl. J. Med.* 325(22):1565-1568 (1991).

DUVAL-VALENTIN, et al., "Specific inhibition of transcription by triple helix-forming oligonucleotides," *Proc Natl Acad Sci U S A.* 89(2):504-8 (1992).

ECKE, et al., "Possible identity of kallikrein binding protein with protein C inhibitor," *Agents Actions Suppl.* 38 (Pt 1):182-9 (1992).

EDGEELL, et al., "Permanent cell line expressing human factor VIII-related antigen established by hybridization," *Proc. Natl. Acad. Sci. (USA)* 80:3734-3737 (1983).

ENGELMAN et al., "Identifying Nonpolar Transbilayer Helices in Amino Acid Sequences of Membrane Proteins," *Annu. Rev. Biophys. Chem.* 15:321-53 (1986).

ESMON & OWEN, "Identification of an endothelial cell cofactor for thrombin-catalyzed activation of protein C," *Proc. Natl. Acad. Sci. (USA)* 78(4):2249-2252 (1981).

ESMON & SCHWARZ, "An Update on Clinical and Basic Aspects of the Protein C Anticoagulant Pathway," *Trends Cardiovasc. Med.* 5(4):141-148 (1995).

ESMON, "Factors regulating the inhibition of thrombin by antithrombin III," in Chemistry and Biology of Thrombin, R. L. Lundblad, J. W. Fenton, II, and K. G. Mann, editors. Ann Arbor Science, Ann Arbor., 403-411 (1977).

ESMON, "Protein S and Protein C - Biochemistry, Physiology, and Clinical Manifestation of Deficiencies," *Trends Cardiovasc. Med.* 2(6):214-220 (1992).

ESMON, "The Roles of Protein C and Thrombomodulin in the Regulation of Blood Coagulation," *J. Biol. Chem.* 264(9):4743-4746 (1989).

ESMON, et al., "Complex Formation Between Thrombin Thrombomodulin Inhibits Both Thrombin-catalyzed Fibrin Formation and Factor V Activation," *J. Biol. Chem.* 257(14):7944-7947 (1982).

ESMON, et al., "Protein C Activation," *Methods Enzymol.* 222:359-385 (1993).

FUKUDOME & ESMON, "Identification, Cloning, and Regulation of a Novel Endothelial Cell Protein C/Activated Protein C Receptor*," *J. Biol. Chem.* 269(42):26486-26491 (1994).

FUKUDOME, et al., "Identification, Cloning, and Regulation of a Novel Endothelial Cell Protein C/Activated Protein C Receptor," *Circulation* 90(4):I133 (1994).

FUKUDOME & ESMON, "Molecular Cloning and Expression of Murine and Bovine Endothelial Cell Protein C/Activated Protein C Receptor (EPCR) - The Structural and Functional Conservation in Human, Bovine and Murine EPCR*," *J. Biol. Chem.* 270(10):5571-5577 (1995).

GALVIN, et al., "Reconstitution of Rabbit Thrombomodulin Into Phospholipid Vesicles," *J. Biol. Chem.* 262(5):2199-2205 (1987).

GERSON, et al., "Severe Acquired Protein C Deficiency in Purpura Fulminans Associated with Disseminated Intravascular Coagulation: Treatment with Protein C Concentrate," *Pediatrics* 91(2):418-422 (1993).

GRAHAM, et al., "A new technique for the assay of infectivity of human adenovirus 5 DNA.," *Virology*. 52(2):456-67 (1973).

GREGORIADIS, "Liposomes," in Drug Carriers in Biology and Medicine, Chap. 14. pp. 287-341 (Academic Press, 1979).

GREY, et al., "Selective effects of protein C on activation of human monocytes by lipopolysaccharide, interferon-gamma, or PMA: modulation of effects on CD11b and CD14 but not CD25 or CD54 induction," *Transplant Proc.* 25(5):2913-4 (1993).

GRIGORIEV, et al., "A triple helix-forming oligonucleotide-intercalator conjugate acts as a transcriptional repressor via inhibition of NF kappa B binding to interleukin-2 receptor alpha-regulatory sequence," *J Biol Chem* 267(5):3389-95 (1992).

GRINELL, et al., "Human protein C inhibits selectin-mediated cell adhesion: role of unique fucosylated oligosaccharide," *Glycobiology* 4(2):221-5 (1994).

HEANEY, et al., "Membrane-associated and soluble granulocyte/macrophage-colony - stimulating factor receptor α subunits are independently regulated in HL-60 cells," *Proc. Natl. Acad. Sci. U.S.A.* 92:2365-2369 (1995).

HEANEY & GOLDE, "Soluble cytokine receptors," *Blood* 87(3):847-857 (1996).

HOFSTEENGE, et al., "Effect of thrombomodulin on the kinetics of the interaction of thrombin with substrates and inhibitors," *Biochem. J.* 237:243-251 (1986).

HOGG, et al., "Identification of structural domains in protein C involved in its interaction with thrombin-thrombomodulin on the surface of endothelial cells," *J Biol Chem* 267(2):703-6 (1992).

HOLT, et al., "An oligomer complementary to c-myc mRNA inhibits proliferation of HL-60 promyelocytic cells and induces differentiation," *Mol Cell Biol.* 8(2):963-73 (1988).

HORIUCHI, et al., "Soluble interleukin-6 receptors released from T cell or granulocyte/macrophage cell lines and human peripheral blood mononuclear cells are generated through an alternative splicing mechanism," *Eur. J. Immunol.* 24:1945-1948 (1994).

ISHII & MAJERUS, "Thrombomodulin is Present in Human Plasma and Urine," *J. Clin. Invest.* 76:2178-2181 (1985).

ITAKURA, et al., "Synthesis and Use of Synthetic Oligonucleotides," in *Ann. Rev. Biochem.* 53:323-356 (1984).

JACKMAN, et al., "Human thrombomodulin gene is intron depleted: Nucleic acid sequences of the cDNA and gene predict protein structure and suggest sites of regulatory control," *Proc. Natl. Acad. Sci. (USA)* 84:6425-6429 (1987).

JIANG, et al., "Nucleocytoplasmic transport is enhanced concomitant with nuclear accumulation of epidermal growth factor (EGF) binding activity in both 3T3-1 and EGF receptor reconstituted NR-6 fibroblasts," *J. Cell Biol.* 110:559-568 (1990).

KABAT, et al., *Sequences of Proteins of Immunological Interest*, 4th Ed. (U.S. Dept. Health and Human Services, Bethesda, MD, 1987)

KAISHO, et al., "BST-1, a surface molecule of bone marrow stromal cell lines that facilitates pre-B-cell growth," *Proc Natl Acad Sci U S A.* 91(12):5325-9 (1994).

KAPIOTIS, et al., "Interleukin-4 counteracts pyrogen-induced downregulation of thrombomodulin in cultured human vascular endothelial cells," *Blood.* 78(2):410-5 (1991).

KOZAK, et al., "Point mutations define a sequence flanking the AUG initiator codon that modulates translation by eukaryotic ribosomes," *Cell* 44(2):283-92 (1986).

KYTE, et al., "A simple method for displaying the hydropathic character of a protein," *J Mol Biol* 157(1):105-32 (1982).

LAEMMLI, "Cleavage of Structural Proteins During the Assembly of the Head of Bacteriophage T4," *Nature*, 227:680-685 (1970).

LASZIK, et al., "The Human Protein C Receptor Is Present Primarily on Endothelium of Large Blood Vessels," *Circulation*, 96(10):1-9 (1997).

LE BONNIEC, et al., "The role of calcium ions in factor X activation by thrombin E192Q," *J Biol Chem* 267(10):6970-6 (1992).

LEDBETTER, et al., "Covalent association between human thymus leukemia-like antigens and CD8(Tp32) molecules," *J Immunol* 134(6):4250-4 (1985).

LENTZ, et al., "Regulation of Thrombomodulin by Tumor Necrosis Factor- α : Comparison of Transcriptional and Posttranscriptional Mechanisms," *Blood* 77(3):543-550, (1991).

LEWIS, et al., "Automated site-directed drug design: the concept of spacer skeletons for primary structure generation," *Proc. R. Soc. Lond.*, 236(1283):125-140 (1989)

LEWIS, et al., "Automated site-directed drug design: the formation of molecular templates in primary structure generation," *Proc. R. Soc. Lond.*, 236(1283):141-162 (1989)

LOBIE, et al. "Nuclear translocation and anchorage of the growth hormone receptor," *J. Biol. Chem.* 269:31735-31746 (1994).

LU, et al., "The Active Site of the Thrombin-Thrombomodulin Complex - A Fluorescence Energy Transfer Measurement of its Distance Above the Membrane Surface*," *J. Biol. Chem.* 264(22):12956-12962 (1989).

LUST, et al., "Isolation of An mRNA Encoding a Soluble Form of the Human Interleukin-6 Receptor," *Cytokine* 4(2):96-100 (1992).

MACIAG, et al., "An endothelial cell growth factor from bovine hypothalamus: identification and partial characterization," *Proc Natl Acad Sci U S A.* 76(11):5674-8 (1979).

MAHER, et al., "Inhibition of DNA binding proteins by oligonucleotide-directed triple helix formation.," *Science* 245(4919):725-30 (1989).

MAHER, "Nuclear Translocation of fibroblast growth factor (FGF) receptors in response to FGF-2," *J. Cell Biol.* 134:529-536 (1996).

MARUYAMA, et al., "Increased expression of thrombomodulin on the cultured human umbilical vein endothelial cells and mouse hemangioma cells by cyclic AMP," *Thromb Res.* 61(3):301-10 (1991).

MATHER, et al., "The 2.8 Å Crystal Structure of Gla-Domainless Activated Protein C," *EMBO J.* 15(24):6822-6831 (1996).

MATHEWS, "Structure of a Nonadecapeptide of the Fifth EGF Domain of Thrombomodulin Complexed with Thrombin," *Biochemistry* 33:13547-13552 (1994).

MCKINLAY, et al., "Rational Design of Antiviral Agents," *Annual Review of Pharmacology and Toxicology*, 29:111-122 (1989)

MERRIFIELD, "Solid-Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide," *J. Am. Chem. Soc.* 85:2149-2154 (1964).

MIZUSHIMA, et al., "pEF-BOS, a powerful mammalian expression vector," *Nucleic Acids Res.* 18(17):5322 (1990).

MOORE, et al., "Tumor Necrosis Factor Leads to the Internalization and Degradation of Thrombosis from the Surface of Bovine Aortic Endothelial Cells in Culture," *Blood* 73(1):159-165 (1989).

MÜLLBERG, et al., "The Soluble Human IL-6 Receptor," *J. Immunol.* 152:4958-4968 (1994).

MULLIGAN, et al., "The basic science of gene therapy," *Science* 260(5110):926-32 (1993)

NARANG, et al., "Chemical Synthesis of Deoxyoligonucleotides by the Modified Triester Method," in *Methods Enzymol.* 65:610-620 (1980).

NAWROTH, et al., "Modulation of endothelial cell hemostatic properties by tumor necrosis factor," *J Exp Med.* 163(3):740-5 (1986).

OFFENSPERGER, et al., "In Vivo inhibition of duck hepatitis B virus replication and gene expression by phosphorothioate modified antisense oligodeoxynucleotides," *EMBO J.* 12(3):1257-1262 (1993).

OHDAMA, et al., "Plasma Thrombomodulin in Wegener's Granulomatosis as an Indicator of Vascular Injuries," *Chest* 106:666-671 (1994).

OLSEN, et al., "Ca²⁺ dependence of the interactions between protein C, thrombin, and the elastase fragment of thrombomodulin. Analysis by ultracentrifugation," *Biochemistry* 31(3):746-54 (1992).

ORSON, et al., "Oligonucleotide inhibition of IL2R alpha mRNA transcription by promoter region collinear triplex formation in lymphocytes," *Nucleic Acids Res* 19(12):3435-41 (1991).

OWEN, et al., "The Conversion of Prothrombin to Thrombin," *J. Biol. Chem.* 249(2):594-605 (1974).

PANJA, et al., "CD1d is involved in T cell-intestinal epithelial cell interactions," *J Exp Med.* 178(3):1115-9 (1993).

PARKINSON, et al., "Stable Expression of a Secretable Deletion Mutant of Recombinant Human Thrombomodulin in Mammalian Cells," *J. Biol. Chem.* 265(21):12602-12610 (1990).

PERRY & DAVIES, QSAR: Quantitative Structure-Activity Relationships in Drug Design pp. 189-193 (Alan R. Liss, inc. 1989)

PORCELLI, et al., "CD1b restricts the response of human CD4-8- T lymphocytes to a microbial antigen," *Nature.* 360(6404):593-7 (1992).

POSTEL, et al., "Evidence that a triplex-forming oligodeoxyribonucleotide binds to the c-myc promoter in HeLa cells, thereby reducing c-myc mRNA levels," *Proc Natl Acad Sci U S A.* 88(18):8227-31 (1991).

PROUDFOOT, et al., "3' non-coding region sequences in eukaryotic messenger RNA," *Nature* 263(5574):211-4 (1976).

QUEHENBERGER, et al., "Increased Levels of Activated Factor VII and Decreased Plasma Protein S Activity and Circulating Thrombomodulin During Use of Oral Contraceptives," *Thromb. Haemost.* 76:729-734 (1996).

REGAN, et al., "The endothelial cell protein C receptor. Inhibition of activated protein C anticoagulant function without modulation of reaction with proteinase inhibitors," *J. Biol. Chem.* 271, 17499-17503 (1996).

REITSMA, et al., "Protein C Deficiency: A Database of Mutations, 1995 Update," *Thromb. Haemost.* 73:876-879 (1995).

REZAIE, et al., "Communication: Protein C Inhibitor Is a Potent Inhibitor of the Thrombin-Thrombomodulin Complex," *J. Biol. Chem.* 270(43):25336-25339 (1995).

RIPKA, "Computers Picture the Perfect Drug," *New Scientist*, 54-57 (June 16, 1988)

ROLLINS, et al., "Inhibition of Homologous Complement by CD59 is Mediated by a Species-Selective Recognition Conferred Through Binding to C8 Within C5b-8 or C9 Within C5b-9," *J. Immunol.* 146(7):2345-2351 (1991).

ROTHBARTH, et al., "cDNA-derived molecular characteristics and antibodies to a new centrosome-associated and G2/M phase-prevalent protein," *J Cell Sci.* 104 (Pt 1):19-30 (1993.).

ROUVINEN, et al., "Computer-Aided Drug Design," *Acta Pharmaceutica Fennica*, 97:159-166 (1988)

SADLER, et al., "Structure-Function Relationships of the Thrombin-Thrombomodulin Interaction," *Haemostasis* 23(suppl 1):183-193 (1993).

SARIN, et al., "Inhibition of acquired immunodeficiency syndrome virus by oligodeoxynucleoside methylphosphonates," *Proc. Natl. Acad. Sci. USA* 85(20):7448-7794 (1989).

SEBESTYÉN, et al., "DNA vector chemistry: the covalent attachment of signal peptides to plasmid DNA," *Nature Biotechnology* 16, 80-85 (1998).

SELIGSOHN, et al., "Homozygous Protein C Deficiency Manifested by Massive Venous Thrombosis in the Newborn," *N. Engl. J. Med.* 310(9):559-562 (1984).

SHAW, et al., "Modified deoxyoligonucleotides stable to exonuclease degradation in serum," *Nucleic Acids Res.* 19(4):747-750 (1991).

STEARNS, et al., "The Interaction of a Ca^{2+} -dependent Monoclonal Antibody with the Protein C Activation Peptide Region," *J. Biol. Chem.* 263(2):826-832 (1988).

STEARNS-KUROSAWA, et al., "The endothelial cell protein C receptor augments protein C activation by the thrombin-thrombomodulin complex," *Proc. Natl. Acad. Sci. (USA)* 93:10212-10216 (1996).

STERN, et al., "Cultured bovine aortic endothelial cells promote activated protein C-protein S-mediated inactivation of factor Va," *J Biol Chem* 261(2):713-8 (1986).

SUZUKI, et al., "Structure and expression of human thrombomodulin, a thrombin receptor on endothelium acting as a cofactor for protein C activation," *EMBO J.* 6(7):1891-1897 (1987).

SZOSTAK, "In Vitro genetics," *TIBS* 19:89-93 (1992).

TAKAHASHI, et al., "Circulating Thrombomodulin As a Novel Endothelial Cell Marker: Comparison of Its Behavior with von Willebrand Factor and Tissue Type Plasminogen Activator," *Am. J. Hematol.* 41:32-39 (1992).

TAKAHASHI, et al., "Circulating Thrombomodulin in Thrombotic Thrombocytopenic Purpura," *Am. J. Hematol.* 38:174-177 (1991).

TAKANO, et al., "Plasma Thrombomodulin in Health and Diseases," *Blood.* 76(10):2024-2029 (1990).

TANAKA, et al., "Increased Thrombomodulin Values in Plasma of Diabetic Men with Microangiopathy," *Clin. Chem.* 37(2):269-272 (1991).

TAYLOR, et al., "C4b-Binding Protein Exacerbates the Host Response to *Escherichia coli*," *Blood* 78(2):357-363 (1991).

TAYLOR, et al., "Protein C Prevents the Coagulopathic and Lethal Effects of *Escherichia coli* Infusion in the Baboon," *J. Clin. Invest.* 79:918-925 (1987).

VON HEIJNE, "A New Method for Predicting Signal Sequence Cleavage Sites," *Nucleic Acids Res.* 14(11):4683-4690 (1986).

WADA, et al., "Plasma Thrombomodulin as a Marker of Vascular Disorders in Thrombotic Thrombocytopenic Purpura and Disseminated Intravascular Coagulation," *Am. J. Hematol.* 39:20-24 (1992).

WEN, et al., "Human Thrombomodulin: Complete cDNA Sequence and Chromosome Localization of the Gene," *Biochemistry* 26:4350-4357 (1987).

WICKSTROM, et al., "Human promyelocytic leukemia HL-60 cell proliferation and c-myc protein expression are inhibited by an antisense pentadecadeoxynucleotide targeted against c-myc mRNA," *Proc Natl Acad Sci U S A.* 85(4):1028-32 (1988).

WILLIAMS, et al., "The immunoglobulin superfamily--domains for cell surface recognition.," *Annu Rev Immunol* 6:381-405 (1988).

XIE, et al., "Nuclear localization of p185neu tyrosine kinase and its association with transcriptional transactivation," *Biochem. Biophys. Res. Comm.* 203:1589-1598 (1994).

YE, et al., "The Active Site of Thrombin is Altered Upon Binding to Thrombomodulin - Two Distinct Structural Changes are Detected by Fluorescence, but only one Correlates with Protein C Activation," *J. Biol. Chem.* 266(34):23016-23021 (1991).

YE, et al., "The Fifth and Sixth Growth Factor-like Domains of Thrombomodulin Bind to the Anion-binding Exosite of Thrombin and Alter Its Specificity," *J. Biol. Chem.* 267(16):11023-11028 (1992).

YOUNG, et al., "Triple helix formation inhibits transcription elongation in vitro," *Proc Natl Acad Sci U S A.* 88(22):10023-6 (1991).

ZAMECNIK, et al., "Inhibition of replication and expression of human T-cell lymphotropic virus type III in cultured cells by exogenous synthetic oligonucleotides complementary to viral RNA," *Proc Natl Acad Sci U S A.* 83(12):4143-6 (1986).

ZAMECNIK, et al., "Inhibition of Rous sarcoma virus replication and cell transformation by a specific oligodeoxynucleotide," *Proc Natl Acad Sci U S A.* 75:280-284 (1978).

ZHU, et al., "Systemic gene expression after intravenous DNA delivery into adult mice," *Science* 261(5118):209-11 (1993).

Remarks

This statement should not be interpreted as a representation that an exhaustive search has been conducted or that no better art exists. Moreover, Applicants invite the Examiner to make an independent evaluation of the cited art to determine its relevance to the subject matter of the

U.S.S.N.: Divisional of 09/182,616
Filed: August 20, 1999
INFORMATION DISCLOSURE STATEMENT

present application. Applicants are of the opinion that their claims patentably distinguish over the art referred to herein, either alone or in combination.

Respectfully submitted,



Patrea L. Pabst
Reg. No. 31,284

Date: August 20, 1999

ARNALL GOLDEN & GREGORY, LLP
2800 One Atlantic Center
1201 W. Peachtree Street
Atlanta, Georgia 30309-3450
(404) 873-8794
(404) 873-8795 (fax)